

REMARKS

Reconsideration of the Office Action mailed June 6, 2000, (hereinafter the "present Office Action") and allowance of the application, as amended, are respectfully requested.

In the present Office Action, claims 1-21, 40 and 65 are listed as pending and claims 1-21, 40 and 65 are listed as rejected. Applicants have amended claims 1 and 21 to place the application in better condition for allowance.

1. The Examiner has maintained the restriction requirement and made it final.
2. The Examiner has rejected claims 1-21, 40 and 65 under 35 U.S.C. §112, second paragraph. In particular, the Examiner took issue to the use of the term "or" in lines 7-8 of claim 1 arguing that the phrase "said first solution comprises acetone, acetonitrile, ethyl acetate, tetrahydrofuran, or glyme" was unclear. Applicants respectfully traverse this rejection, but, in an attempt to clarify the invention recited in the pending claims, have amended claim 1 as detailed above. The Examiner's position that the use of the term "or" renders a claim indefinite *per se* is not supported. To the contrary, "alternative expressions using "or" are acceptable, such as 'wherein R is A, B, C or D.'" See, M.P.E.P. 2173.05(h)(II) and *In re Gaubert*, 524 F.2d 1222, 187 USPQ 664 (CCPA 1975). Therefore, claim 1 as amended and claims 5 and 8 as written are

clear and definite. Accordingly, the rejection of claims 1, 5 and 8 over 35 U.S.C. §112, second paragraph, is obviated and should be withdrawn.

3. The Examiner has rejected claim 21 under 35 U.S.C. §112, second paragraph, noting that "vacuum drying" lacks sufficient antecedent basis. In reply thereto and to place the application in a better condition for allowance, Applicants have amended claim 21 to eliminate the need for an antecedent basis. Applicants aver that said amendment did not introduce new matter and is fully supported by the submitted Specification. Accordingly, the rejection of claim 21 under 35 U.S.C. §112, second paragraph, is obviated and should be withdrawn.

4-5. The Examiner rejected claims 1-10, 12-21, 40 and 65 under 35 U.S.C. §102(b) over WO 94/15587 (hereinafter "the '587 reference"). Applicants respectfully traverse this rejection. The Court of Appeals for the Federal Circuit, in ruling on the standard for anticipation under 35 U.S.C. §102(b), opined:

[i]t is elementary that an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice or device.

See *In re Donohue*, 226 U.S.P.Q. 619, 621 (1985); and

...exclusion of a claimed element from a prior art reference is enough to negate anticipation by that reference.

See *Atlas Power Co. v. E. I. duPont DeNemours & Co.*, 224 U.S.P.Q. 409, 411 (1984). With the foregoing in mind, Applicants request that the Examiner consider the following argument.

Without conceding the correctness of the Examiner's rejection and solely to advance the application towards allowance, Applicants have amended claim 1. In particular, the limitation of claim 2 has been imported into claim 1 to reflect that a distinguishing feature of the present invention is that the first solution is added to first liquid in the form of small droplets. Applicants submit that no such limitation is disclosed in the '587 reference. Contrary to the Examiner's position, use of a teflon filter, as disclosed in the '587 reference, to inject a first solution into a second solution does not produce small droplets. Accordingly, claim 1, as amended, includes a limitation which is not disclosed by the '587 reference. As such, since the '587 reference lacks a limitation expressed in claim 1 of the present application, the '597 reference can not anticipate amended claim 1 nor any claim dependent thereon (i.e. claims 3-10, 12-21, 40 and 65). The rejection of claims 1, 3-10, 12-21, 40 and 65 under 35 U.S.C. §102(b) over WO94/15587 is therefore obviated. Applicants respectfully request that said rejection be withdrawn.

6-7. The Examiner has rejected claims 1-21, 40 and 65 under 35 U.S.C. §103(a) as being unpatentable over Shalaby et al (WO 94/15587 hereinafter "the '587 reference"). Applicants respectfully traverse this rejection. The '587 reference fails to teach or suggest the claimed method of the present application as amended, i.e. the addition of the first solution to the first liquid as small droplets. Accordingly, the rejection of claims 1-

21, 40 and 65 under 35 U.S.C. §103(a) over the '587 reference should be withdrawn.

8. The Examiner rejected claims 1-21, 40 and 65 under 35 U.S.C. § 103(a) as being unpatentable over Shalaby et al ("the '587 reference") in view of Khan et al. WO 93/17668 (hereinafter "the '668 reference"). Specifically, the Examiner alleges that the '668 reference teaches:

...formation of microparticles using frozen non-solvent such as ethanol (paragraph bridging pages 8 and 9) to extract the solvent for the polymer as the frozen microspheres thaw.

Accordingly, it would be obvious to one skilled in the art at the time of the invention to maintain the non-solvent alcohol (first liquid wherein the conjugate is not soluble) of the step in the '587 reference where the acetone/peptide-polymer solution is injected into alcohol at a temperature that is below the freezing temperature of the polymer/active agent solution with the expectation that doing so would allow for extraction of the solvent and a motivation being a desire to remove the solvent from the microspheres.

Applicants respectfully traverse this rejection on several grounds.

First, Applicants assert that the now-claimed method does not employ a frozen (i.e., solid) solvent of any sort. None of the Examples presented involve temperatures that would cause the solvents to freeze. In fact, the experimental techniques (i.e., stirring, atomizing, etc.) utilized in the disclosed Examples could not be employed with frozen solvents. Second, the '668 reference teaches the formation of microparticles by atomizing the polymer/active agent into a liquefied gas. Such a procedure

would require extreme temperatures to achieve the desired results. Third, the '668 reference teaches that "the drug [must not] react with the polymeric matrix so as to inactivate or bind the drug." See, the '668 reference page 2, line 35 to page 3 line 1. The present invention, however, involves "a method of making microparticles of a sustained release conjugate containing a free carboxyl group-containing biodegradable polymer ... and a free amino group-containing drug *which are ionically bonded to each other*. See, page 1 line 22 to page 2 line 1. "An invention that otherwise might be viewed as an obvious modification of the prior art will not be deemed obvious in a patent law sense when one or more prior art references "teach away" from the invention. See, *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 26 USPQ2d 1923, 1927 (Fed. Cir. 1990).. Fourth, the '668 reference specifically dissuades using solvent evaporation. "Solvent evaporation works reasonable well but is not preferred since the amount of incorporated material is usually lower than the theoretical values *due to loss of drug to the aqueous phase*." See, the '668 reference, page 7, lines 12-15. The present application specifically provides for use of water as a solvent, see, page 2, line 10, and is not concerned with the presence of water. See Example 6 and Claim 13 et. seq. As such, the '668 reference again "teaches away" from the present invention. Gillette Co.,

F.2d at 720. Finally, and most persuasive, one skilled in the art would not be motivated to combine the teachings of the '587 reference with the '668 reference because the latter teaches that

...It is important to select a solvent for the polymer having a higher melting point than the non-solvent for the polymer so that the non-solvent melts first, allowing the frozen microspheres to sink into the liquid where they later thaw. If a cold liquid non-solvent system for making the polymeric microspheres is used, the microspheres will sink immediately into the non-solvent.

As the polymer solvent containing polymer-peptide microparticles sink into the thawed non-solvent, they in turn thaw, which allows for the extraction of the polymer solvent from the polymer-peptide conjugate. The '587 reference employs acetone as the polymer solvent and water as the non-solvent. See Example 11 of the '587 reference. Since acetone has a lower melting point (-93.35°C) than water, as the temperature is raised, the frozen acetone would melt before the frozen water, resulting in a scenario that is contrary to that required by the '668 reference. In other words, if the teachings of the '668 reference were applied to the teachings of the '587 reference as suggested by the Examiner, the acetone encapsulating the peptide-polymer would melt and re-dissolve the polymer before the ice would begin to melt. The foregoing clearly illustrates the incompatibility of the '587 and '668 references. Accordingly, no motivation exists to combine said references.

Accordingly, the rejection of claims 1, 3-21, 40 and 65 under 35 U.S.C. §103(a) over '587 in view of '668 is obviated and should be withdrawn.

Applicants respectfully submit that all pending claims herein are now in condition for allowance. Should Examiner Ware deem that any further action by the Applicants would be desirable in placing this

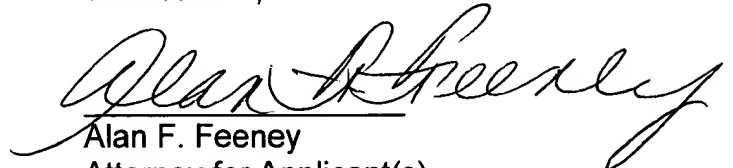
application in a better condition for issue, he is requested to telephone Applicants' undersigned representative.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No.50-0590.

Respectfully submitted,

Biomeasure, Inc.

Nov. 6, 2000
Date


Alan F. Feeney
Attorney for Applicant(s)
Reg. No. 43,609

27 Maple Street
Milford, MA 01757-3650
Telephone: (508) 478-0144
Facsimile: (508) 473-3531